
Heteroplasmy of Mouse mtDNA Is Genetically Unstable and Results in Altered Behavior and Cognition.

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Authors: Mark S Sharpley, Christine Marciniak, Kristin Eckel-Mahan, Meagan McManus, Marco Crimi, Katrina Waymire, Chun Shi Lin, Satoru Masubuchi, Nicole Friend, Maya Koike, Dimitra Chalkia, Grant Macgregor, Paolo Sassone-Corsi, Douglas C Wallace

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Scientific Abstract:

Maternal inheritance of mtDNA is the rule in most animals, but the reasons for this pattern remain unclear. To investigate the consequence of overriding uniparental inheritance, we generated mice containing an admixture (heteroplasmy) of NZB and 129S6 mtDNAs in the presence of a congenic C57BL/6J nuclear background. Analysis of the segregation of the two mtDNAs across subsequent maternal generations revealed that proportion of NZB mtDNA was preferentially reduced. Ultimately, this segregation process produced NZB-129 heteroplasmic mice and their NZB or 129 mtDNA homoplasmic counterparts. Phenotypic comparison of these three mtDNA lines demonstrated that the NZB-129 heteroplasmic mice, but neither homoplasmic counterpart, had reduced activity, food intake, respiratory exchange ratio; accentuated stress response; and cognitive impairment. Therefore, admixture of two normal but different mouse mtDNAs can be genetically unstable and can produce adverse physiological effects, factors that may explain the advantage of uniparental inheritance of mtDNA.

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